REMARKS/ARGUMENTS

The foregoing amendments of the claims are fully supported by the specification and claims as filed and do not add new matter. Applicants believe that the current amendments place all claims in *prima facie* condition for allowance or, at least, in a better form for consideration on appeal. Accordingly, the consideration and entry of the present amendment after final rejection is respectfully requested.

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional, or continuation-in-part applications.

Claims 32-34, 36, 37 and 41-70 are pending in this application.

I. Claim Rejections Under 35 U.S.C. §101

Claims 32-34, 36, 37 and 41-70 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is directed to non-statutory subject matter." In particular, the Examiner asserts that the claims cover a method of using a human "female mammal" in Claims 32 and 63, and that the recitation of producing "at least one mammal" in Claim 63 covers humans.

Applicants have amended Claims 32 and 63 to recite non-human female mammals and methods of producing non-human transgenic mammals as per the Examiner's suggestion. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. §101 has been obviated by amendment and should be withdrawn.

II. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 32-34, 36, 37 and 41-70 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner has asserted three separate scope of enablement rejections. In particular, the Examiner first asserts that the specification "fails to provide an enabling disclosure for the claimed method of making a transgenic mammal because the specification does not teach specific phenotypic alterations as a result of the various genetic modifications contemplated." (Page 3 of the instant Office Action). The Examiner further asserts that the specification "fails to provide an enabling disclosure for making any type of genetic modification" because allegedly "[w]hile the specification enables single base substitutions, no guidance is provided for making other types of changes to the genome (Pages 3-4 of the instant Office Action). Finally, the Examiner asserts that the

specification "fails to provide an enabling disclosure for making targeted changes to any mammal other than the mouse" because allegedly "recA-catalyzed gene targeting has not been shown to be as efficient as random integration in any species other than mouse." (Page 4 of the instant Office Action).

First of all, Applicants respectfully maintain the position that the specification provide enablement for the claimed subject matter for the reasons previously set forth in Applicants' Response filed January 24, 2005. With respect to the latter two objections, the specification clearly discloses that the methods of the present invention may be used, for example, to insert entire genes into specifically selected sites of the target genome. The reference by Maga *et al.*, previously submitted in Applicants' Response filed January 24, 2005, demonstrates that the claimed methods, involving the use of RecA protein, work to increase transgene integration frequencies in farm mammals. In addition, the USPTO has already established as fully enabled Applicants' methods for targeting and altering by homologous recombination a pre-selected target DNA sequence in any eukaryotic cell, as demonstrated by Claim 1 of U.S. Patent No. 5,763,240, to which the instant application claims priority.

The Examiner appears to concede that the specification *does* in fact teach how to make the recited transgenic mammals, stating that "the enablement requirement is not satisfied by addressing only the how to make prong of the enablement requirement because the specification must also teach how to use the claimed invention. A method of making has use only if the product made has a use and one of skill in the art would know how to use the product made." (Page 8 of the instant Office Action). The Examiner asserts that "[t]he use of a eukaryotic cell is substantially different from the use of a transgenic mammal and the instant specification does not teach how to use the wide variety of transgenic animals covered by the claims." (Page 8 of the instant Office Action).

The Examiner's statements that Applicants have not taught how to use the recited transgenic mammals are based upon the assertion that "the skilled artisan would only know how to use a transgenic animal that has a useful phenotype. However, for reasons of record, the phenotype of a transgenic mammal is unpredictable and therefore the preparation of a useful (and therefore enabled) transgenic mammal is likewise unpredictable." (Page 7 of the instant Office Action). Thus all three prongs of the enablement rejection are based on the initial assertion that

the specification has allegedly not taught specific phenotypic alterations as a result of the various genetic modifications contemplated.

Applicants respectfully submit that the Examiner is applying a standard for enablement that is inconsistent with both existing case law and the precedent set established by claims that have already been issued by the USPTO. As previously discussed in Applicants' Response filed January 24, 2005, the claims are generic to, and read on, any user-desired phenotype. Applicants reiterate that there is no requirement that methods of transgenesis must be claimed in association with any "particular phenotype." Were this the case, the claims of numerous issued patents, as cited in Applicants' previous response, would be invalid. Applicants respectfully submit that the instant Office Action provides no arguments or evidence as to how the cited issued claims may be distinguished from the instant claims as being enabled while the instant claims are not.

The question is not whether Applicants are permitted to claim improved methods that are broad to any desired phenotype, but rather, whether Applicants' specification, coupled with information known in the art, is sufficient to enable Applicants' methods across a sufficient number of genetic (not phenotypic) alterations to meet the requirements of 35 U.S.C. §112, first paragraph. Applicants respectfully submit that this is the case, and that the Examiner has provide no evidence to suggest otherwise. Accordingly, the Examiner has failed to establish a *prima facie* case of lack of enablement.

The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[1] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[2,3]
As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[4] The Examiner has provided no evidence that one of skill in the art could not practice the claimed methods without

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[1] *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976).

[2] *In re Colianni*, 561 F.2d 220, 224, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977).

[3] M.P.E.P. §2164.06.

[4] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers,* 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F 2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

engaging in undue experimentation beyond that typical in the art.

One of ordinary skill in the art would understand that the transgenic mammals produced by the claimed methods have many possible uses. The desired phenotype depends upon the intended use and may include, for example, disease symptoms if the goal is to produce an animal model of a human disease, a wild-type phenotype if the goal is to correct a disorder, or the presence of a specific protein in the animal's milk, if the goal is to produce this protein. The skilled artisan would understand how to test for the desired phenotype using methods well known in the art for testing transgenic animals.

The Examiner appears to argue that the art is so unpredictable that one of skill in the art would not be able to obtain any specific phenotype using the claimed methods. This assertion is factually inaccurate. For example, the Examiner asserts that the recA-mediated gene targeting method disclosed in the specification can result in random as well as site-specific integration, and that "methods for preventing or detecting random integration events are not disclosed." (Page 5 of the instant Office Action). This assertion is factually incorrect, as the specification provides ample guidance for verifying the desired homologous recombination. The specification also provides methods for verifying the expression of the altered mRNA in target cells. See, for example, Example 3 of the specification which describes both PCR and Southern blot techniques for verifying homologous recombination and mRNA expression (pages 74-78), or Example 6, which describes analyses performed on samples derived from tail biopsies of transgenic mice (page 97). Thus the specification has clearly described how to verify that the techniques result in the desired specific targeted gene alterations, as well as the expression of the altered gene at the mRNA level.

The Examiner further asserts that it is "difficult to design transgenes with predictable behavior" and argues in support of this assertion that several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. (Pages 5-6 of the instant Office Action). Applicants note that, as discussed above, use as animal models for human diseases is only one of the asserted utilities for transgenic animals produced by the claimed methods. Applicants further respectfully submit that to assert that the claims to improved methods of transgenesis are not enabled unless Applicants have also taught precisely how to determine the utility of each transgenic animal produced by the method is akin to

asserting that an improved method of nucleic acid sequencing would not be enabled without providing methods to test each sequenced gene to determine its utility. Clearly gene sequencing is an extremely useful general method for identifying genes that, once sequenced, have a wide range of utilities. Similarly, the claimed methods are useful general methods to produce transgenic mammals that, once produced, may be used for a range of purposes.

The Examiner's allusion to *Brenner v. Manson,* that "a method of making a product has use only if the product made has use," is not relevant here. *Brenner* concerns a narrow exception to the general rule that inventions are useful. In *Brenner*, the claimed invention was a process for making one particular synthetic steroid. Some steroids are useful, but most are not. While the claimed process in *Brenner* produced a composition that bore homology to some useful steroids, antitumor agents, it also bore structural homology to a substantial number of steroids having no utility at all. There was no evidence that could show, by substantial likelihood, that the steroid produced by the claimed method was not just as useless as the majority of steroids. In contrast, the methods claimed in the instant application are generic methods that can be used to produce transgenic mammals having any desired genotypic alteration. It is indisputable that these methods can be used to produce transgenic mammals having utility.

The Examiner has acknowledged that the specification teaches how to make the recited transgenic mammals using the claimed methods. One of ordinary skill in the art would also understand how to use the claimed methods, based upon the guidance provided in the specification and in the art known at the time of filing. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

III. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 32-34, 36, 37 and 41-70 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner asserts that "Claims 32-34, 36, 37 and 41-70 remain indefinite with regard to the 'modified endogenous nucleic acid' because it is unclear relative to what standard or point of reference the endogenous nucleic acid is considered to be 'modified'. Furthermore , it is unclear what would be regarded as an "endogenous nucleic acid'." (Page 9 of the instant Office Action).

Applicants respectfully submit that "targeted endogenous DNA sequence" is defined in the specification as "polynucleotide sequences contained in a target cell." (see page 22, lines 28-29). Thus it would be clear to one of ordinary skill in the art that the nucleic acid is modified compared to the original sequence present in the target cell to be modified. The specification further defines the types of sequences regarded as "endogenous," making clear that "endogenous" nucleic acids include, for example, genes originally derived from an exogenous source such as a virus. (See the specification at page 22, line 28 to page 23, line 18).

Accordingly, the metes and bounds of the claims are clear, and withdrawal of the rejection of Claims 32-34, 36, 37 and 41-70 under 35 U.S.C. §112, second paragraph, is respectfully requested.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

In the event that this office action is not entered or does not result in an allowance of the application, applicants file herewith a Notice of Appeal (attached).

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **41428-0380 US-4**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 3, 2005

By: _____
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